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Recent Advances in Primary Immunodeficiencies: Identification of Novel Genetic Defects and Unanticipated Phenotypes

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ABSTRACT: Primary immunodeficiencies (PIDs) have traditionally been defined according to their immunologic phenotype. Far from being concluded, the search for human genes that, when mutated, cause PID is actively being pursued. During the last year, four novel genetic defects that cause severe combined immunodeficiency and severe congenital neutropenia have been identified. At the same time, the immunologic definition of primary immunodeficiencies has been expanded by the recognition that genetic defects affecting innate immunity may result in selective predisposition to certain infections, such as mycobacterial disease, herpes simplex encephalitis, and invasive pneumococcal infections. Studies of genetically determined susceptibility to infections have recently shown that immunologic defects may also account for novel infectious phenotypes, such as malaria or leprosy. Finally, a growing body of evidence indicates that primary immunodeficiencies may present with a noninfectious clinical phenotype that may be restricted to single organs, as in the case of atypical hemolytic uremic syndrome or pulmonary alveolar proteinosis. Overall, these achievements highlight the importance of human models, which often differ from the corresponding animal models. **(*Pediatr Res* 65: 3R–12R, 2009)**

For many years, "classical primary immunodeficiencies," in which broad susceptibility to infections is due to mutations of a single gene, have represented a unique model to identify gene products that play a key role in initiating, maintaining, or regulating immune function. The study of diseases such as severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), chronic granulomatous disease (CGD), and many more has led to better understanding of the mechanisms that are involved in development and function of T and B lymphocytes and of phagocytic cells. Since 1952, when unique susceptibility to recurrent infections was linked to lack of serum gammaglobulins (1), and for more than 30 y, primary immunodeficiencies (PID) were mainly defined in terms of clinical and immunologic phenotype. The careful analysis of the pattern of inheritance of PIDs, and the availability of more potent immunologic tools, such as MAb and sophisticated assays to explore the phenotype and function of immune cells, have helped identify an unexpected heterogeneity within clinically homogeneous forms of PID. For example, both X-linked and autosomal recessive forms of SCID have been identified; furthermore, it became clear that—while retaining similar clinical features and the consistent lack of circulating T cells—infants with SCID may or may not present deficiencies also of B and/or NK lymphocytes (2). Similarly, X-linked and autosomal recessive forms of congenital agammaglobulinemia and of CGD were disclosed.

The heterogeneity of PIDs was further illustrated when advances in molecular genetics and the development of the Human Genome Project made cloning of PID-causing genes feasible. Yet, many forms of PID are still "orphan" as to the genetic defects responsible for their phenotype. For example, the genetic defect underlying common variable immune deficiency (CVID) is known in only 5–10% of the cases (3).

At the same time, the phenotypic paradigm of PIDs has been challenged. In particular, rather than focusing on the classical PIDs (in which patients are prone to multiple infections by various organisms), many groups have started to focus on cohorts of patients with an increased sensitivity (or resistance) to specific infectious pathogens. This was largely contributed by phenomenal work of Casanova *et al.* (reviewed in Refs. 4–7s). Furthermore, it has become apparent that defects in immune-related genes may lead to clinical phenotypes other than susceptibility to infections, thus broadening the clinical paradigm of PIDs.

In this review, we will focus on recent advances in the genetic characterization of classical PIDs and of novel forms of PIDs associated with a restricted susceptibility to infections or with a noninfectious clinical phenotype.

Identification of novel genetic defects underlying "classical" forms of PID. Since 1993, when the Bruton Tyrosine

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Abbreviations: AK2, adenylate kinase 2; **aHUS,** atypical hemolytic uremic syndrome; **APECED,** autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; **BTK,** bruton tyrosine kinase; **CGD,** chronic granulomatous disease; **CVID,** common variable immune deficiency; **DNA-PKcs,** DNA-protein kinase catalytic subunit; **ER,** endoplasmic reticulum; **IRAK-4,** interleukin-1 receptor-associated kinase-4; **IFN,** interferon; **MAC,** membrane attack complex; **MSMD,** Mendelian susceptibility to mycobacterial disease; **PAP,** pulmonary alveolar proteinosis; **PID,** primary immunodeficiency; **RD,** reticular dysgenesis; **SCID,** severe combined immunodeficiency; **TLR,** toll like receptor; **WAS,** Wiskott-Aldrich syndrome; **WHIM,** warts, hypogammaglobulinemia,infections, and myelokathexis syndrome; **XLA,** X-linked agammaglobulinemia; **XLP,** X-linked lymphoproliferative disease

Kinase (*BTK*) gene, whose mutations account for XLA, was cloned (8,9), more than 100 genes responsible for primary immunodeficiency diseases have been identified (10). This explosion of gene discoveries for many groups of PIDs might have suggested the gene hunting was over (11). As a matter of fact, identification of human genes that, when mutated, cause PID has continued, as demonstrated by a series of recent discoveries.

Novel genetic defects that cause combined immune deficiency. During the last months, three novel genetic defects that account for combined immunodeficiency in humans have been identified.

Using genome-wide linkage analysis in three consanguineous families, two groups of investigators have established that mutations in the adenylate kinase 2 (*AK2*) gene are responsible for reticular dysgenesis (RD), a rare autosomal recessive form of SCID, associated with profound neutropenia and sensorineural deafness (12,13). The *AK2* gene defects identified in patients with RD resulted in absence or severe reduction of protein expression. AK2 is expressed in the mitochondrial intermembrane space in several tissues, and it regulates the levels of adenosine diphosphate by catalyzing the reversible transfer of a phosphoryl group from adenosine triphosphate to adenosine monophosphate. Although most cells in the body express both AK2 and AK1, blood nucleated cells express AK2, but have little if any AK1 protein (13). Therefore, leukocytes may be particularly sensitive to AK2 deficiency. It has been suggested that the normal AK2 protein may play a critical role in providing the energy required for proliferation of hematopoietic progenitors and/or in controlling cell apoptosis. In this regard, it is interesting to observe that Kostmann disease (the prototype of severe congenital neutropenia) is due to deficiency of HAX-1, another protein located in the mitochondrial intermembrane space, which is required to prevent apoptosis in myeloid, lymphoid, and neuronal cells (14).

In keeping with the putative role played by AK2 in hematopoiesis, transduction of bone marrow $CD34^+$ cells from RD patients with normal *AK2* cDNA-encoding lentiviral vector restored generation of mature myeloid cells of the neutrophil lineage *in vitro*, whereas down-regulation of *AK2* expression in normal $CD34^+$ cells by lentiviral-mediated gene transfer of *AK2* short hairpin RNA resulted in a profound arrest in myeloid differentiation (12). On the other hand, induction of an aberrant *ak2* splicing in zebrafish resulted in complete absence of developing T lymphocytes (13).

Lagresle-Peyrou *et al.* have also offered important insights into the pathophysiology of deafness associated with RD. Using confocal microscopy, they have shown that in the inner ear, AK2 is located within the lumen of the stria vascularis capillaries (12), suggesting that here it could function as an ectoenzyme. Because serum adenosine diphosphate has deleterious effects on endothelial integrity, it is possible that *AK2* mutations may cause damage to the inner ear microvessels and hence cause the sensorineural damage of RD.

In another seminal article, van der Burg *et al.* (15) have identified the first case of SCID due to mutations of the *PRKDC* gene, coding for DNA-protein kinase catalytic subunit (DNA-PKcs). This is a critical factor for V(D)J recombination, a process that is essential in generating T and B lymphocytes and that involves both lymphoid-specific gene products (RAG1, RAG2) and a series of ubiquitously expressed factors involved in DNA repair (Ku70/80, DNA-PKcs, Artemis, Cernunnos/XLF, DNA ligase IV). A variety of genetic defects (RAG1, RAG2, Artemis, Cernunnos/XLF, DNA ligase IV) that impair this process and result in combined immunodeficiency had been demonstrated in humans (16). With the notable exception of Cernunnos/XLF defect (that is associated with a leaky phenotype), and of DNA ligase IV deficiency (whose phenotype may range from SCID to minimal immunodeficiency), most of these defects, when complete, are associated with the inability to generate both T and B lymphocytes (and hence cause T^-B^- SCID). Importantly, defects of V(D)J recombination may associate with normal (as in the case of RAG defects) or increased (Artemis, Cernunnos/XLF, DNA ligase IV deficiency) cellular radiosensitivity, the latter reflecting impaired DNA repair. Recently, van der Burg *et al.* (15) have identified the first patient with radiosensitive SCID with a mutation in the *PRKDC* gene, encoding for DNA-PKcs. It is interesting to note that mutations of DNA-PKcs in mice account for the naturally occurring *scid* phenotype, which is known since many years (17). Furthermore, mutations of the same gene are responsible for a severe immunodeficiency phenotype also in other animal species, such as Arabian foals and Jack Russell terriers (18). The delay with which mutations in the same gene have been identified in humans may at first sight seem surprising. However, it should be considered that the *PRKDC* gene includes 86 exons, making attempts to identify mutation by direct sequencing cumbersome. For this reason, several groups have relied on other screening assays, in particular on protein expression analysis, without success. Interestingly, the *PRKDC* mutation identified by van der Burg *et al.* (15) is a missense mutation that does not interfere with DNA-PKcs protein expression, kinase activity, or DNA end-binding capacity, but affects the quality of coding joins (with long stretches of P nucleotides) and overall end-joining activity. This observation reinforces the importance of developing functional assays that may help identify gene defects that cause PID without interfering with protein expression.

Upon completion of differentiation into $CD4^+$ or $CD8^+$ single positive thymocytes, newly generated naive T cells egress the thymus and traffic to secondary lymphoid organs in the periphery. A recent study has shown that coronin 1A, an actin regulator of the coronin family that is predominantly expressed in hematopoietic cells, plays a major role in this process (19). This protein associates with and inhibits the actin-nucleation promoting activity of the Arp2/3 complex. Cyster and coworkers (19) have shown that mice with a recessive peripheral T-cell deficiency (*Ptcd*) carry a homozygous missense mutation in the Coronin 1A (*Coro1a*) gene, which results in increased inhibition of the Arp2/3 complex and impaired thymic egress. Furthermore, they showed that both *Coro1a*-deficient mice and another strain of mice with a hypomorphic *Coro1a* gene defect generated using *N*-ethyl-*N*-nitrosourea-induced mutagenesis, share features of increased

levels of F-actin in thymocytes, reduced number of thymocytes due to increased apoptosis, and significant peripheral T-cell lymphopenia. These observations prompted the authors to search for possible defects of the *CORO1A* gene in patients with atypical combined immunodeficiency. One such patient with $T^-B^+NK^+$ combined immunodeficiency was identified, who carried a deletion of the *CORO1A* gene on one allele and a dinucleotide deletion resulting in frameshift and premature termination, on the other allele. Western-blot analysis showed absence of coronin 1A protein expression in Epstein-Barr-virus-transformed B cells. The patient presented relatively late (at 13 mo of age) with severe vaccine-related varicella and was successfully treated by hematopoietic cell transplantation (19). This study is important because it provides the first example of SCID due to defects in the regulation of actin polymerization in thymocytes and thus expands the mechanisms of SCID pathophysiology in humans (Table 1). Interestingly, reduced T cell numbers are also observed in patients with the Wiskott-Aldrich syndrome (WAS), another disorder of regulation of actin polymerization (20). Although it is not clear why coronin 1A deficiency results in decreased cell survival, this study has opened the interesting perspective that other cases of severe T-cell deficiency may be due to mutations in *CORO1A* or in other genes that regulate actin polymerization in the T-cell compartment.

A novel genetic defect links glucose metabolism to myeloid development. Severe congenital neutropenia (SCN) represents another example of genetically heterogeneous conditions for which significant advances in the characterization of the molecular pathophysiology have been recently achieved (21,22). In some forms of SCN, such as defects of *ELA2* and *HAX1* genes, neutropenia is associated with spontaneous apoptosis of mature neutrophils (14,23,24). Increased genomic instability has been reported also in myeloid precursors from patients with SCN due to activating mutations in the *WASP* gene (25). Finally, one subgroup of patients in whom SCN is associated with a defect of glucose metabolism (glycogenosis 1b), carry mutations in the *SLC37A4* gene, encoding for the glucose-6 phosphate transporter into the endoplasmic reticulum (26,27). Klein *et al.* (28) have recently identified a novel molecular defect that accounts for SCN. Boztug *et al.* have studied two consanguineous pedigrees of Arameic descent that included five patients with a unique phenotype consisting of SCN associated with congenital heart disease and abnormally visible s.c. veins and/or venous angiectasias. Using a whole genome mapping approach, the authors have identified a candidate region on the long arm of chromosome 17. Sequencing of candidate genes in the interval has shown that all five affected patients carried a homozygous missense mutations in the *G6PC3* gene that encodes for the ubiquitously expressed glucose-6 phosphatase catalytic subunit 3. They have demonstrated that the mutation identified in the patients abrogates enzymatic activity and results in decreased glucose levels in the endoplasmic reticulum (ER). This biochemical abnormality promotes ER stress, induces dephosphorylation of glycogen synthase kinase 3-β (GSK3β), and as a consequence of this, causes phosphorylation and proteasome-mediated degradation of the anti-apoptotic factor Mcl-1. In keeping with this, patients' neutrophils and bone marrow myeloid precursors showed increased apoptosis that could be rescued upon retrovirus-mediated transfer of the *G6PC3* gene into patients' hematopoietic progenitor cells. To investigate what proportion of SCN patients with an undefined genetic defect may carry mutations in the *G6PC3* gene, the authors have screened 104 subjects, and identified biallelic mutations of *G6PC3* in seven of them. They have also confirmed that *G6PC3* mutations result in a complex phenotype, in which SCN is most often associated with congenital heart disease, abnormal s.c. vein visibility or angiectasias, and urogenital defects. This study is important for several reasons. It has shed light on the mechanisms that link glucose metabolism to apoptosis in myeloid cells and has thus provided an elegant explanation also for the SCN phenotype of patients with glycogenosis 1b, because in this disease defects of the glucose-6 phosphate transporter also result in decreased levels of glucose in the ER. Furthermore, it has reinforced the notion that careful analysis of human patients (especially if from restricted ethnic groups) may lead to identify novel clinical phenotypes that may prove critical to unravel the molecular cause of genetically determined disorders.

Table 1. *Pathophysiology mechanisms that account for severe combined immune deficiency (SCID) (Refs. 20–27)*

Disease mechanism	Gene defects
Increased apoptosis	
due to mitochondrial energy failure	*AK2*
due to accumulation of toxic metabolites	*ADA*
due to abnormal actin polymerization	*CORO1A*
Impaired cytokine-mediated signaling	
due to defects of the common γ chain	*IL2RG* (X-linked SCID)
due to defects of the IL-7R α chain	*IL7R*
due to defects of JAK3	*JAK3*
Impaired signaling through the pre-T cell receptor	
due to defective V(D)J recombination	*RAG1, RAG2, DCLRE1C, LIG4*, PRKDC*
due to impaired expression of CD3 subunits	*CD3D, CD3E, CD3Z*
Impaired signaling in the periphery	*ORAI1*
Unknown mechanism	*RMRP**

*These gene defects are most often associated with a milder clinical phenotype than SCID.

Primary immunodeficiencies with a restricted susceptibility to infections. In the last few years, mainly because of seminal contributions by Casanova *et al.*, several PIDs have been reported that are characterized by susceptibility to a restricted number of pathogens (Table 2) (29–41). Here, we will review the pathophysiology of some of these novel forms of PID.

Mendelian susceptibility to mycobacterial disease (MSMD). Mendelian susceptibility to mycobacterial disease (MSMD) was originally described in the early 1950s (42), but

Table 2. *Predisposition to specific infections in humans*

Pathogen	Presentation	Affected gene/ Chromosomal region	Functional defect	Notes	Reference
Bacteria					
S. pneumoniae	Invasive disease	*IRAK-4, MyD88*	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as *S. aureus*	29, 30
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency		31, 32
	Invasive disease, poor prognosis	*PFC*	Properdin deficiency		
Mycobacteria	MSMD	*IL12B*, *IL12RB1*, *IKBKG*	Impaired IFNγ response to IL-12/23	Also susceptible to *Salmonella typhi* infections	4, 33
		IFNGR1, IFNGR2, *STAT1*	Impaired cellular response to IFNγ		
Mycobacterium leprae	Leprosy	*PARK2*	Unknown	Possible E3-ubiquitin ligase dysfunction	106
		LTA	Unknown		101
Viruses					
Herpes simplex (type 1)	*Herpes Simplex Encephalitis*	*UNC93B1, TLR3*	Impaired production of type I IFNs	STAT-1 and NEMO deficiency also predispose to HSV infections, amongst other infections	34, 35
Epstein–Barr virus	XLP	*SH2D1A*	SAP deficiency	Fulminant infectious mononucleosis, Malignant and non-malignant	36
		XIAP/BIRC4	XIAP deficiency	lymphoproliferative disorders, dysgammaglubulinemia, autoimmunity	37
Human Papillomaviruses	Epidermodysplasia Verruciformis	*EVER1/TMC6*	EVER1 deficiency		38, 39
		EVER2/TMC8	EVER2 deficiency		
	WHIM	*CXCR4*	Truncated CXCR4	Altered neutrophil mobilization, T-cell lymphopenia. recurrent bacterial respiratory infections chronic cutaneous/genital papilloma virus disease	40
Parasites					
Plasmodium falciparum	Malaria fever episodes	10p15	Unknown	Linkage studies	89, 91
	Severe Malaria	*GNAS*	Unknown	SNP Association studies	91
	Severe Malaria	*IFNR1*	Unknown	SNP Association studies	90
Schistosoma mansoni	Intensity of infection	5q31-q33	Unknown		92
	Hepatic fibrosis	6q22-q23, *IFNR1*	Unknown		93
Leishmania donovani	Visceral leishmaniasis (Kala-Azar)	22q12 2q35 (*NRAMP1*)	Unknown		95–97
Yeast					
Candida	APECED, Chronic candidiasis	Aire	Unknown	APS-1-chronic candidiasis, chronic hypoparathyroidism, Addison's disease	41

TLR, Toll-like receptor; MAC, membrane attack complex; MSMD, Mendelian susceptibility to mycobacterial disease; IFN, Interferon; XLP, X-linked lymphoproliferative disease; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy.

its cellular and molecular pathophysiology has remained largely undefined until recently. In the past 12 y, six genes that encode for proteins involved in the IL-12/IL-23-dependent IFNγ-mediated immunity were shown to be associated with MSMD, including *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, and *IKBKG* (33,43). Interestingly, apart from being susceptible to marginally virulent mycobacterial strains, such as environmental mycobacteria or BCG vaccine strains, and to *Salmonella* infections, patients with MSMD are otherwise healthy and are not susceptible to other infectious pathogens. This group of MSMD-causing genes can be grouped into genes that elicit IFN-γ responses through IL-12/IL-23 (*IL12B*, *IL12RB1*, and *IKBKG*) and genes that determine the cellular responsiveness to IFN-γ (*IFNGR1*, *IFNGR2*, and *STAT1*).

The first genetic etiology of MSMD to be discovered was represented by mutations of *IFNGR1*, encoding the ligand-binding chain of the IFN-γ receptor (44,45). Later, mutations in the *IFNGR2* gene, encoding for the second chain of the IFN-γ receptor, and mutations of *STAT1*, which encodes for a transcription factor activated by IFN-γ receptor engagement, were also described in patients with MSMD (46,47). Importantly, mutations in these genes result in a different severity of the clinical phenotype, depending on the residual cellular ability to respond to IFN-γ. In particular, complete IFN-γR1 deficiency, inherited as an autosomal recessive (AR) trait, typically results in death during early childhood, whereas autosomal dominant partial IFN-γR1 deficiency most often presents later in life (44,45,48–51).

A similar phenotypic variability has been described for *IFNGR2* deficiency (3). Patients with loss-of-expression mutations (46), or with mutations resulting in surface-expressed, nonfunctional IFNGR2 molecules (52,53) have a worse clinical phenotype than patients with hypomorphic *IFNGR2* mutations resulting in residual responsiveness to IFN-γ (54).

STAT1 mutations are even more interesting because different mutations lead to significantly different clinical phenotypes. Although patients with homozygous *STAT1* mutations that abrogate protein expression are susceptible to both mycobacterial and severe viral infections that result in death in the first years of life (33,55,56), patients with *STAT1* mutations that affect the DNA-binding domain (57) or impair STAT1 phosphorylation (47), show selective susceptibility to mycobacterial, but not to viral, infections. This heterogeneity of clinical phenotype results from the fact that complete STAT1 deficiency leads to cellular unresponsiveness to both type I (IFN-α and IFN-β) and type II (IFN-γ) IFN, whereas mutations that affect STAT1 function result in an impaired response to IFN-γ but spare cellular responsiveness to IFN-α/β.

The clinical phenotype of MSMD patients with defects in the IL-12/IL-23 pathway differs from the phenotype observed in patients with defects of the IFN-γ receptor pathway because the former manifest susceptibility not only to mycobacterial, but also to *Salmonella* infections that occur in up to 50% of patients (58,59). Defects in the IL-12/IL-23 pathway, and specifically *IL12RB1* gene defects, are the most prevalent cause of MSMD. The *IL12RB1* gene encodes IL-12Rβ1, a receptor subunit that is shared by IL-12 and IL-23 receptors. Similarly, the *IL12B* gene, whose mutations account for a minority of cases of MSMD (58,60), encodes for the p40 subunit that is shared by IL-12 and IL-23 cytokines.

Another component of the cellular response that leads to IFN-γ production is represented by the NF-kB essential modulator (NEMO), a regulatory component of the NF-kB signaling pathway, that is activated in response to various stimuli, including signaling through CD40, Toll-like receptors (TLRs), IL-1R, and tumor necrosis factor-α receptor. NEMO is encoded by the X-linked *IKBKG* gene. Heterozygous null mutations in this gene are associated with incontinentia pigmenti in females, whereas hypomorphic mutations in males lead to X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency (XR-EDA-ID) (61–63). Almost all patients with *IKBKG* mutations described to date present variable levels of impaired host defenses, with severe susceptibility not only to mycobacterial disease, but also to Gram-positive and Gram-negative pyogenic bacteria. This reflects both defects of specific antibody production (with or without hypogammaglobulinemia) and impairment of activation of CD40- and TLR-dependent pathways in dendritic cells and macrophages (62,64). In particular, impairment of CD40-mediated IL-12/IL-23 production in patients with *IKBKG* mutations is responsible for the X-linked form of MSMD (65).

Predisposition to herpes simplex encephalitis (HSE). Herpes simplex infections affect most individuals. It has been estimated that 60–95% of the entire population become HSV-seropositive by adulthood (66,67). HSV infection may be asymptomatic or may present with a spectrum of clinical manifestation ranging from skin infection to severe, potentially fatal, systemic disease. Herpes simplex encephalitis (HSE) is typically caused by HSV type 1 (HSV-1) and follows a bimodal distribution, with one third of cases occurring in childhood and one half in individuals aged 50 y or more (68). This distribution probably reflects primary HSV infection in the younger age group and reactivation of latent HSV infection in the elderly. The mortality rate of HSE is as high as 70% if untreated (69–71), and although it has significantly dropped after introduction of acyclovir therapy, many patients develop neurologic sequelae (70).

Although it had been recognized that patients with significant primary or secondary cellular immunodeficiencies are susceptible to HSE, only a minority of patients with HSE had demonstrable immunodeficiency, when evaluated by conventional assays.

As mentioned above, patients with complete STAT-1 deficiency have impaired cellular responsiveness to both IFN-γ and to IFN-α/β. Therefore, they show increased susceptibility not only to mycobacterial disease but also to viral infections, including HSE (56). Similarly, a case of severe HSE was reported in a patient with NEMO deficiency, which also interferes with IFN responses (72). However, both in STAT1-deficient and in the NEMO-deficient patients, increased susceptibility to HSV infections (including HSE) was not the only infectious clinical phenotype. Overall, the reason why only some individuals—even within the same family—show unique susceptibility to severe and recurrent HSE has remained unclear until recently, when Casanova *et al.* have

established that this phenotype may be due to defects of the *UNC93B1* and the *TLR3* genes.

Casrouge *et al.* (34) have described two patients with HSE, who were homozygous for *UNC93B1* mutations that resulted in impaired cellular IFN-α/β and IFN-λ antiviral responses. UNC-93B is a transmembrane protein that is predominantly retained in the ER, where it may bind to both Toll-like receptor (TLR)-3 and TLR9 (73). More recently, Casanova *et al.* have shown that HSE may occur in TLR3 deficiency (35). TLR3 is located in the endosomal compartment and recognizes double-stranded RNA that is produced by many viruses during replication (64,74). Fibroblasts from TLR3- or UNC93B1-deficient patients show impaired production of type I IFN and increased apoptosis after stimulation with poly(I:C) (a TLR3 ligand) or HSV-1 (35). Overall, UNC93B1 and TLR3 deficiencies are two clinical "experiments" of nature that demonstrate the critical role that signaling through TLR3-UNC-93B plays in the response to primary HSV-1 infection by inducing production of type I IFNs. Yet, even after identification of these patients, only a minute proportion of patients with increased susceptibility to HSE have a defined genetic defect, suggesting that mutations of other genes, along the same or in different cellular pathways, remain to be identified.

Susceptibility to pyogenic bacteria and specifically to pneumococcal infections. Until the introduction of the pneumococcal vaccine, *Streptococcus pneumoniae* was considered the most common bacterial pathogen that caused a variety of infections in childhood, including pneumonia, otitis media, meningitis, osteomyelitis, and sepsis (75). Susceptibility to invasive pneumococcal disease may be contributed by several conditions, such as secondary immunodeficiency (HIV infection, chemotherapy), physical disruption of the upper respiratory tract epithelium (as observed after viral respiratory tract infections), anatomical or functional asplenia, as well as several classical PID, including antibody deficiencies (as in XLA), WAS, and some complement deficiencies (5,7,75,76). However, all of these situations contribute to susceptibility to other pathogens as well. In contrast, recent studies have demonstrated that specific gene abnormalities may lead to a restricted susceptibility to pyogenic bacterial infections and pneumococcal infections in particular.

The IL-1 receptor-associated kinase-4 (IRAK-4), a serine threonine kinase that acts downstream to TLRs and IL-1 receptor, was shown to be deficient in patients with selective susceptibility to *S. pneumoniae* and *S. aureus* infections (76,77). More than 30 IRAK4-deficient patients have been described to date (29,76–91). IRAK4 deficiency results in impaired production of inflammatory cytokines after TLR stimulation. This phenomenon explains the mild inflammatory response elicited *in vivo* in these patients.

IRAK-4 is selectively recruited to TLRs and IL-1R by the adaptor protein MyD88. Recently, MyD88 was found to be deficient in a group of nine children that suffered from life-threatening, recurrent pyogenic bacterial infections, including invasive pneumococcal disease (30). Patients with IRAK4 or MyD88 deficiency are not susceptible to severe viral infections, because IFN-α/β and IFN-λ production in response to TLR3 and TLR4 stimulation does not require IRAK-4 (91). Importantly, although IRAK-4 and MyD88 deficiency may lead to invasive and potentially life-threatening infections in childhood, their clinical phenotype tends to improve with age, even without antibiotic prophylaxis, possibly reflecting development of adaptive immunity (86). Thus, IRAK4 and MyD88 deficiencies represent challenges to the paradigm of classical PIDs. In fact, the fact that their clinical phenotype spontaneously improves with age contrasts with the observation that in the absence of appropriate treatment, classical forms of PIDs are typically characterized by progressive worsening of the clinical phenotype.

Extending the paradigm of PID with predisposition to selected pathogens: Searching for susceptibility genes in targeted regional areas. The history of PIDs has been largely based on studies performed in Western countries that have a defined—although variable—microbial ecosystem. However, after the recognition that PIDs may be also characterized by selective predisposition to certain pathogens (mycobacteria, herpes simplex, pyogenic bacteria, etc.), it is logical to assume that similar unique predisposition to other pathogens that are largely confined to certain geographical areas may exist. Recent evidence supports this notion.

Predisposition to parasitic infections (malaria, schistosoma, and leishmania). Observations regarding susceptibility and resistance to malaria have been studied for many years. Red blood cell disorders such as sickle cell anemia and the carrier status for thalassemia have been shown to provide an evolutionary selective advantage by protecting from malaria (92). Classical genetic studies such as twin studies and linkage analysis proved the major role of host genetic factors, especially in children (93–95). The major histocompatibility complex as well as a cytokine-gene cluster on chromosome 5q31-q33 were also shown to associate with susceptibility/resistance to malaria (96,97). Recently, with the advance in genome-wide scanning and association, analysis a genome-wide linkage analysis was performed on 241 malaria susceptible siblings from 68 selected families from Ghana, West Africa, who were exposed to hyperendemic malaria transmission and were homozygous wild type for the established malaria resistance factors of Hb (Hb)S, HbC, alpha$^+$ thalassemia, and glucose-6-phosphate-dehydrogenase deficiency (98). Several regions showed significant linkage to certain parasitological and clinical phenotypes such as a linkage of a region on chromosome 10p15 with malaria fever episodes.

Within the chromosome 21q22.11 region previously associated with severe malaria, Khor *et al.* (99) identified a single-nucleotide polymorphism (*IFNAR1* 272354c-g) at position −576 of the interferon alpha receptor 1 (*IFNAR1*) gene, which was found to be strongly associated with susceptibility to severe malaria.

Another recent study demonstrated an association between severe malaria and certain single nucleotide polymorphisms (SNPs) in the gene for the G-protein alpha subunit that was previously shown to interact with the malaria parasite in a cellular level (100).

A genome-wide scan preformed on a large cohort in Brazil localized a locus controlling the intensity of infection by *Schistosoma mansoni* on chromosome 5q31-q33 (101). A

region containing *IFNGR1* was linked to pathology due to *S. mansoni* and especially Schistosomal hepatic fibrosis (102). Association studies have also provided evidence for major histocompatibility complex control of pathology in schistosomiasis (103).

Similar studies have shown linkage of other loci to other parasites and to severe infection, such as the reports regarding visceral Leishmniasis (104–107).

Overall, these studies support the hypothesis that mutations or polymorphisms in several genes can lead to susceptability to various parasitic infections, hence forming a new group of previously unrecognized PIDs.

Predisposition to leprosy. According to the World Health Organization, the global registered prevalence of leprosy at the beginning of 2008 stood at 212,802 cases (108). Leprosy is an infectious disease caused by *Mycobacterium leprae*; yet, certain genetic factors may predispose to infection and/or influence the clinical course (43,109,110). Twin studies, studies of familial clusters and segregation analysis, suggested a polygenic inheritance with major susceptibility genes (reviewed in Ref. 110).

Several linkage studies have suggested target loci in chromosome regions 6q25-q26, 6p21, 10p13, and 20p12-p13 to play a role in the susceptibility to leprosy or its manifestations (111–114). The chromosome 6q25 locus that was mapped in Vietnamese patients for susceptibility to leprosy was further analyzed using multiple SNP studies to point out the putative *PARK2* promoter overlapping the 5′-region of the adjacent *PACRG* gene (115). *PARK2* was discovered and characterized as culprit for early onset Parkinson's disease (116). It encodes an E3-ubiquitin ligase that plays an important role in controlling proteolysis and possibly in the regulation of immune responses (117).

Using a similar positional cloning approach, a second leprosy susceptibility gene, Lymphotoxin alpha (*LTA*) coded on chromosome 6p21, was identified. LTA interacts with Lymphotoxin beta (LTB) to create the agonist for the LTB receptor. This interaction is critical for secondary lymphoid organ development and for host defense against intracellular pathogens (110).

These interesting findings, the first of which was the first successful study to use positional cloning to localize a major gene in a common infectious disease (117) suggest that leprosy is actually a PID in which certain gene defects predispose their carriers to both susceptibility to infection by *M. leprae* and to the development of the clinical picture (7,110).

Primary immunodeficiencies: Not only infections. Traditionally, PIDs have been defined on the basis of increased susceptibility to infections. This paradigm has been challenged by a growing series of observations that defects of immune genes may lead to clinical phenotypes unrelated to susceptibility to infections. One example of PIDs without an infectious phenotype is represented by endothelial damage due to altered regulation and/or function of the complement system.

Hemolytic uremic syndrome (HUS) is characterized by severe damage of the glomerular endothelium and is most often preceded by diarrhea caused by verocytotoxin-producing bacteria, usually *Escherichia coli* O157:H7. However, in a minority of cases, HUS is unrelated to preceding infections and may occur as a familial trait. It has been shown that these cases of atypical HUS (aHUS) are due to complement dysregulation, specifically a gain of function of the alternative pathway, due to mutations in complement regulatory proteins factor H, MCP and factor I, the activator factor B, or the C3 factor (118,119). Mutations that alter the function of the alternative pathway of complement have been also associated with dense deposits glomerulonephritis and age-related macular degeneration (120,121).

Another example of a PID with an organ-limited, infection-independent clinical phenotype is represented by pulmonary alveolar proteinosis (PAP), in which impairment of surfactant homeostasis causes respiratory distress and may lead to respiratory failure. Surfactant is produced by alveolar type II cells. Surfactant aggregates that are released into the alveolar spaces are then uptaken and catabolyzed by alveolar macrophages, in a granulocyte macrophage-colony stimulating factor (GM-CSF)-dependent manner (122). Most often, PAP is due to anti-GM-CSF neutralizing autoantibodies (123). However, two groups have recently established that PAP may also be due to mutations of the *CSF2RA* gene, which is located on the pseudoautosomal region of the X-chromosome and encodes for the α subunit of the GM-CSF receptor (124,125). In patients with *CSF2RA* mutations, surfactant is uptaken by alveolar macrophages, but it is not catabolyzed and hence accumulates intracellularly, resulting in production of the typical foamy alveolar macrophages. These studies establish PAP as a novel PID clinical phenotype and thus broaden the spectrum of the clinical definition of PIDs.

Conclusions

Taken together, the studies of patients with either classical or "atypical" forms of PIDs discussed above illustrate the importance of the human model. Far from being concluded, search for human genes that, when mutated, cause PID is still very active. In fact, several reasons suggest that we have yet to discover many disease-causing genes. In particular, in recent years several genes that account for various "classical" forms of PIDs have been discovered focusing on restricted ethnic groups, with a higher consanguinity rate. Undoubtedly, this success reflects an increased attitude for international collaboration (126). At the same time, these studies have shown the heterogeneity of clinical and immunologic phenotypes that may associate with defects in the same gene. One such example is represented by *RAG* genes mutations, which may cause T^-B^- SCID, Omenn syndrome, leaky SCID, but also granulomas (127,128).

On the other hand, identification of patients with genetically determined susceptibility to selected infections has raised the question of what are the real borders for the definition of PID. Can we expect that all individuals who develop severe or atypical infections by common community acquired pathogens in the absence of other contributory factors (such as chemotherapy, cancer, trauma, etc.) carry mutation in a particular gene? And if so, should these patients be considered affected by PID? Furthermore, does this broad definition of

PID apply only to patients with severe or atypical infections, or should we expand it to include also susceptibility to more common and less severe infections?

Finally, the study of patients with aHUS and with PAP has clearly shown the limitation of a clinical definition of PIDs, based on identification of an infectious phenotype. Indeed, it is becoming more and more obvious that PIDs may present with autoimmune and inflammatory features, or even with previously unanticipated clinical phenotypes that are limited to single organs. With this is mind, it can be expected that a large number of PID genes have yet to be discovered. As mass sequencing, advanced genome-wide scans and bioinformatics become more available and sophisticated, the answer to these questions are on the verge of discovery, as are new approaches to the prevention and treatment of these diseases.

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